REMARKS

Claims 2, 4-7, 9-13 and 15-17 remain in this application. Claims 9 and 11 are withdrawn. Claims 2, 4-7, 9-11 and 13 are currently amended.

Support for the amendments can be found in the specification. No new matter has been added.

CLAIM REJECTIONS - 35 USC § 103

At page 4, the Office Action rejects claims 1-2, 4-8, 10, 12, 13 and 15 under 35 U.S.C. § 103(a) as being unpatentable over KARL et al. (US 2005/0132500) and/or SKOVMAND (WO 01/37662). Applicants respectfully traverse the rejection.

The claimed subject matter is directed to an insecticide composition that contains a non-pyrethroid insecticide in combination with an insect repellent. The non-pyrethroid insecticide is a carbamate insecticide or organophosphate insecticide, and the insect repellent is N,N-diethyl-meta-toluamide (DEET) or 2-(2-hydroxy-ethyl)-piperidine carboxylic acid ester of 1-methyl-propyl (KBR).

The combination of non-pyrethroid insecticide and insect repellent is much more effective than either component when used alone. Thus, in the combination, the concentration of the non-pyrethroid insecticide is lower than its LC100 when it is used alone, and the concentration of the insect repellent is lower than the concentration of the insect repellant procuring

a protective effect when it is used alone. The presently claimed subject matter is also directed to formulations, fabrics, mosquito nets and clothes that contain the insecticide composition.

The Office Action contends that KARL discloses an insecticide composition comprising a mixture of at least one insecticide and/or one repellent, the insecticide being an organophosphorous compound such as pirimiphos-ethyl and pirimiphos-methyl and the repellent being selected from compounds such as N,N-Diethyl-meta-toluamide (DEET). The Office Action further contends that SKOVMAND teaches impregnated netting or fabrics for insect repellence that include an organophosphorous insecticide and/or a repellent such as DEET.

The Office Action acknowledges that KARL et al. and/or SKOVMAND fail to teach a combination of insecticide and repellant at lower concentrations than either used alone, as defined in the present claims. The Office contends, however, that it would have been obvious to one of ordinary skill in the art to combine at least one non-pyrethroid insecticide and at least one insect repellent at the lower concentrations.

The Office appears to rely on general knowledge that combining "insecticidal actives" increases the efficacy of an insecticide such that the maximum level of insects killed for a given application rate of an insecticide is increased, or alternatively, the application rate of an insecticide giving the

maximum level of insects killed can be reduced. The Office contends that one would have been motivated to combine the KARL and SKOVMAND references with this general knowledge in order to obtain the expected benefit of an increase in the efficacy of the claimed insecticide and of having products impregnated with low doses of repellents and insecticide that will last longer due to the combination of the non-pyrethroid insecticide and the repellent. Applicants respectfully disagree with this conclusion.

"Insecticidal active" is a global term to designate two different classes of molecules, i.e., insecticides and repellents. According to the Oxford English Dictionary, the definition of insecticide is "a substance used for killing insects" whereas a repellent is "a substance able to repel a particular thing" (i.e., drive away mosquitoes in the present case). Thus, by combining these two classes of molecules, one of ordinary skill expects two different effects on mosquitoes - driving away mosquitoes and killing those not sensitive to the repellent action.

In its "Guidelines for the Control of Flies Closely Associated with Humans", the World Health Organization gives suitable concentrations of insecticides for space treatment (Copy provided in the Appendix; see, Tables 1 and 2). Most of the compounds listed in this document are also used to impregnate nets to fight against mosquitoes. A listing of eleven pyrethroids

is given in Table 1 and pyrethroid mixtures are presented in Table 2.

Table 1. Suitable insecticides for space treatment for fly control

Insecticide	Chemical Type[a]	Dosage of a.i.[b] (g/ha)	WHO hazard classification of active ingredient (Class)[c]
Chlorpyrifos-methyl	OP	100-150	U
Diazinon	OP	336	II
Dimethoate	OP	224	II
Malathion	OP	672	III
Naled	OP	224	II
Pirimiphos-methyl	OP	250	III
Bioresmethrin	PY	5-10	U
Cypermethrin	PY	2-5	II
Cyphenothrin	PY	5-10	II
d-d-trans-cyphenothrin	PY	2.5-5	NA
Deltamethrin	PY	0.5-1.0	II
Esfenvalerate	PY	2-4	II
Etofenprox	PY	10-20	U
Lambda-cyhalothrin	PY	0.5-1.0	II
Permethrin	PY	5-10	II
d-phenothrin	PY	5-20	U
Resmethrin	PY	2-4	III

[a] OP = organophosphate, PY = pyrethroids.
[b] a.i. = active ingredient.
[c] Class II = moderately hazardous; Class III = slightly hazardous;
Class U= unlikely to pose an acute hazard in normal use; NA = not available.

Table 2: Pyrethroid mixtures used in cold and thermal fog formulations for fly control

Pyrethroid mixtures	Concentration (g a.i.[a]/ha)	
	Cold fog	Thermal fog
Permethrin +	5.0-7.5	5.0-15.0
S-bioallethrin +	0.075-0.75	0.2-2.0
Piperonyl butoxide	5.25-5.75	9.0-17.0
Bioresmethrin +	-	5.5
S-bioallethrin +	-	11.0-17.0
Piperonyl butoxide	-	0-56
Phenothrin +	5.0-12.5	4.0-7.0
Tetramethrin +	2.0-2.5	1.5-16.0
Piperonyl butoxide	5.0-10.0	2.0-48.0
Etofenprox +	5-10	5-10
Pyrethrins +	0.18-0.37	0.18-0.37
Piperonyl butoxide	10-20	10-20
Lambda-cyhalothrin +	0.5	0.5
Tetramethrin +	1.0	1.0
Piperonyl butoxide	1.5	1.5
Cypermethrin +	2.8	2.8
S-bioallethrin +	2	2
Piperonyl butoxide	10	10
Tetramethrin +	12-14	12-14
d-phenothrin	6-7	6-7
d-tetramethin +	1.2-2.5	1.2-2.5
Cyphenothrin	3.7-7.5	3.7-7.5
d-tetramethrin +	1.2-2.5	1.2-2.5
d,d-trans-cyphenothrin	2-8	2-8
Deltamethrin +	0.3-0.7	0.3-0.7
S-bioallethrin +	0.5-1.3	0.16-1.3
Piperonyl butoxide	1.5	1.5

[a] a.i. = active ingredient.

By way of examples, the recommended dosage of permethrin in a combination mixture that includes permethrin is from 5 to 15 g/ha, whereas the recommended dosage of permethrin when used alone is from 5 to 10 g/ha. The recommended dosage of deltamethrin in a combination mixture that includes deltamethrin is from 0.5 to 1.0 g/ha, whereas the recommended dosage of deltamethrin when used alone is from 0.3 to 0.7 g/ha. Hence, it is general knowledge in the art that combining insecticidal actives does not necessarily allow reducing the application rate of an insecticide.

KARL et al. and SKOVMAND disclose compositions including at least one insecticide and/or one repellent and at least one binder. Both references list several different categories of insecticides (e.g., pyrethroid, carbamate and organophosphorous) and repellent. One of ordinary skill in the art would have to choose among 36 non-pyrethroid insecticides (17 carbamate and 19 organophosphorous insecticides) and 18 repellents to determine any combination of insecticide and repellent such as that disclosed in the present application.

Moreover, these references fail to provide any direction to select specific mixture of compounds and to choose specific doses of each of the compounds. Furthermore, each of the embodiments exemplified in the KARL et al. and SKOVMAND references concern pyrethroid insecticides. Thus, one would have to choose between 648 different combinations of non-pyrethroid insecticides and repellents, and to try infinite possible choices of concentrations of these two compounds, in order to arrive at the claimed composition. Contrary to the position taken by the Office Action, one of ordinary skill in the art, in view of the teachings of KARL et al. and SKOVMAND would not have expected any benefit of increased efficacy from the combination of insecticide and repellent in an insecticide composition as presently claimed.

Evidence of the unexpected results of a composition combining pirimiphos-methyl (PM) and DEET are provided in PENNETIER et al. (Malaria Journal (2007) 6:38, p 1-7, copy

provided in the Appendix). In this research, the authors (and inventors Cédric Pennetier and Jean-Marc Hougard) studied interactions between two repellents (DEET and KBR) and the organophosphate insecticide (PM). The study assessed the residual efficacy and inhibition of blood feeding conferred by these mixtures against *Anopheles gambiae* mosquitoes (a malaria vector). The application rate of DEET/KBR was 10 g/m^2 and that for PM was 150 mg/m^2, these dosages being selected as the lower dosages including 100% mortality in the tunnel assay (see, page 3, Treatment).

The research measured the lethal time (LT) and biting inhibition time (BIT). The lethal time corresponds to the mortality rate of mosquitoes whereas biting inhibition time is the blood feeding reduction assessed by comparing the proportion of blood-fed females in treated and control tunnels. Lethal time on mosquitoes (LT_{95} = 95% of killed mosquitoes) of the mixture DEET/PM persists for 87 days, whereas LT_{95} of PM alone is less than 6 days and LT_{95} of DEET alone is less than 3 days. Moreover, the time required to inhibit 95% of the blood feeding (BIT_{95}) is 3 days for PM and 6 days for DEET, whereas BIT_{95} for the mixture DEET/PM is more than one month (37 days).

In the second mixture concerning PM and KBR3023, LT_{95} of the mixture KBR3023/PM persists for 73 days, whereas LT_{95} of PM alone is less than 6 days and LT_{95} of KBR3023 alone is 3 days. Moreover, the BIT_{95} is 3 days for PM and 8 days for KBR3023,

whereas BIT_{95} for the mixture KBR3023/PM is three weeks (21 days). All of these results are summarized in Table 1.

Table 1: Summary statistics for nets treated with Pyrimiphos-methyl (PM 150 mg/m^2), DEET and KBR (both at 10 g/m^2), alone and in combination against susceptible *An. gambiae*. Slope (95% CI), Lethal Time for 50 and 95% (LT_{50-95} in days), Biting Inhibition Time 50 and 95% (BIT_{50-95} in days).

	Mortality						Blood Feeding Inhibition					
insecticide/repellent	slope	(95%CI)	LT_{50}	(95%CI)	LT_{95}	(95%CI)	slope	(95%CI)	BIT_{50}	(95%CI)	BIT_{95}	(95%CI)
PM	-2.29^{ab}	± 0.64	19.67^{a}	± 2.97	5.46^{ab}	± 2.14	-1.33^{a}	± 0.59	25.46^{a}	± 9.33	2.80^{a}	± 2.93
DEET	-1.46^{a}	± 0.40	20.91^{ac}	± 4.75	2.79^{a}	± 1.68	-2.04^{b}	± 0.78	24.38^{a}	± 5.27	5.79^{a}	± 3.44
KBR	-3.04^{b}	± 0.98	24.79^{ac}	± 3.19	9.43^{b}	± 3.17	-2.06^{a}	± 0.81	33.51^{a}	± 7.39	8.03^{a}	± 4.84
PM+DEET	-4.81^{c}	± 0.92	161.03^{b}	± 6.63	87.32^{c}	± 10.84	-3.18^{a}	± 0.90	94.34^{b}	± 7.99	37.44^{b}	± 10.29
PM+DEET expected	-1.37^{a}	± 0.44	31.14^{c}	± 7.56	3.65^{ab}	± 2.66	-1.57^{b}	± 0.60	52.46^{c}	± 12.04	8.09^{a}	± 6.11
PM+KBR	-4.79^{c}	± 0.96	135.39^{b}	± 5.22	73.30^{c}	± 9.46	-2.40^{a}	± 0.67	71.42^{c}	± 8.10	21.04^{bc}	± 7.54
PM+KBR expected	-1.70^{ab}	± 0.54	30.45^{c}	± 6.57	5.41^{ab}	± 3.19	-1.74^{b}	± 0.59	58.09^{c}	± 10.72	10.79^{ac}	± 6.45

Numbers in the same line sharing the same superscript letter do not differ significantly (Confidence intervals are overlapping)

The difference of efficacy between expected and observed LT_{95} and BIT_{95} of DEET/PM or KBR3023/PM indicates a strong synergy between PM and DEET or PM and KBR3023 properties in terms of mortality and blood feeding inhibition. These data clearly demonstrate the interest of a mixture of non-pyrethroid carbamate and organophosphate insecticides (such as PM) and a repellent of DEET or KBR3023.

Accordingly, the inventors of the present application have found a synergy between organophosphorous or carbamate insecticides and repellents such as DEET or KBR3023. When applied the combination is applied together on a mosquito net, the efficacy is higher than the sum of their efficacies (i.e., 1 + 1 = 3). This can be verified by the references of PENNETIER et al. (Amer. J. Trop. Med. Hyg., (2005) 72:6

p 739-744; Malaria Journal (2007) 6:38; copies provided in the Appendix).

Copies of the curriculum vitae of the inventors of the present application, Cédric Pennetier and Jean-Marc Hougard, are provided in the Appendix. The Appendix also includes a brief abstract regarding the Anopheles Biology and Control research network (The ABC Network). This network brings together French and African scientists working in several experimental field stations. The ABC Network is part of the WHO collaborating center for testing insecticides of public health importance. Dr. Pennetier is an active member of the ABC Network.

The synergistic effect for fighting against pest and vector insects is new in regards of the literature and invention. This argument is supported by the recent publication of one mode of action of the repellent DEET, explaining this synergistic effect (CORBEL et al., BMC Biology (2009) 7:47). Indeed, it means that the biological mechanisms underlying this synergistic effect are under investigation and cannot have been known or deduced from any prior publication (most particularly, KARL et al. and SKOVMAND) before the present invention.

Secondary arguments of non obviousness can be found in the technical report series "Malaria Vector Control and Personal Protection" of the World Health Organization, published in 2006. Firstly, concerning the insecticide, the WHO considers that "*the most practical approach to resistance management in residual*

spraying programmes is the rotation of unrelated insecticides according to a pre-arranged plan or the switching of insecticides in response to the results of resistance tests." Also, *"The use of mixtures of unrelated insecticides or treatment of different parts of a net with different insecticides is thought to be promising. The combination of two safe and effective insecticides on the same net offers great potential."*(See, Section 8, page 16). Despite this comprehensive study, the Report provides no teaching about non-pyrethroid insecticides.

Secondly, concerning the insect repellent, the WHO considers that *"Insect repellents such as DEET (N,N-diethyl-3-toluamide) are widely used, especially by travellers in developed and developing countries for protection against mosquito bites. There is skepticism about their use as a malaria prevention measure, the assumption being that application to skin each night requires too much self-discipline for the method to be effective as a public health intervention. Some older trials failed to show any effect, whereas more recent interventions and placebo-controlled trials have shown a clear and substantial effect."* (See, Section 42, page 50). The disadvantages of DEET would have discouraged one of ordinary skill in the art from choosing non-pyrethroid insecticide in combination with DEET as repellent to form insecticidal compositions.

For all of these reasons, and in view of the present amendments, KARL et al. and SKOVMAND fail to teach or suggest,

and would not have rendered obvious, claims 2, 4-7, 12, 13 and 15. Claims 1 and 8 have been canceled. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following items:

- Pennetier et al., Am. J. Trop. Med. Hyg. (2005) 72:6
- Pennetier et al., Malaria Journal (2007) 6:38
- Corbel et al., BMC Biology (2009) 7:47
- World Health Organization, "Guidelines for Control of Flies Closely Associated with Humans"
- World Health Organization, Technical Report Series (2006) "Malaria Vector Control and Personal Protection"
- Curriculum vitae of Cédric Pennetier
- Curriculum vitae of Jean-Marc Hougard
- The ABC Network